

- (f) identifying with respect to the reference sequence one or more of a mutation, a mutation distribution, a mutation frequency, sequence heterogeneity, or DNA damage.
40. The method of claim 39, wherein the sample is derived from a human.
41. The method of claim 39, wherein the sample comprises a tissue sample.
42. The method of claim 39, wherein the sample comprises a blood sample.
43. The method of claim 39, wherein the method comprises detecting mutations or DNA damage that arose in vivo.
44. The method of claim 39, wherein the DNA damaging agent comprises a chemotherapy agent.
45. The method of claim 39, further comprising comparing the first-strand sequencing reads with the second-strand sequencing reads, and generating error-corrected sequences of the double-stranded DNA molecules by distinguishing erroneous nucleotides in one strand that lack a matched base change in the complementary strand.
46. The method of claim 45, further comprising calculating a mutation frequency among the plurality of double-stranded DNA molecules.
47. The method of claim 46, wherein the mutation is a transition mutation.
48. The method of claim 45, wherein an error-corrected sequence maps to the reference sequence, and wherein a sequence difference between the error-corrected sequence and the reference sequence is identified as a true mutation.
49. The method of claim 48, wherein the true mutation is a substitution or insertion mutation type.
50. The method of claim 48, wherein the true mutation is a transition mutation.
51. The method of claim 45, wherein the error-corrected sequences map to the reference sequence, and the method further comprises identifying a distribution of mutations in the double-stranded DNA molecules.
52. The method of claim 49, wherein the error-corrected sequences map to the reference sequence, and the method further comprises identifying a distribution of mutation types in the double-stranded DNA molecules.
53. The method of claim 45, wherein the erroneous nucleotides in one strand that lack a matched base change in the complementary strand are the result of systematic or biological errors in one strand.
54. The method of claim 45, wherein the method comprises determining a genomic distribution of mutations with respect to the reference sequence.
55. The method of claim 54, further comprising identifying mutations common to most cells of a tumor.
56. The method of claim 54, further comprising determining whether a genomic distribution of mutations is a random distribution.
57. The method of claim 39, further comprising comparing the first-strand sequencing reads with the second-strand sequencing reads to generate error-corrected sequences, and reconstructing original double-stranded DNA sequences from the error-corrected sequences.
58. The method of claim 39, wherein the double-stranded DNA molecules comprise a deaminated cytosine.
59. The method of claim 58, wherein the method further comprises enzymatically treating the double-stranded DNA molecules to repair damaged ends thereof prior to the ligating.
60. The method of claim 39, further comprising purifying a plurality of cypher-target nucleic acid complexes prior to sequencing, wherein the purified cypher-target nucleic acid complexes comprise nucleic acid molecules from specific genomic regions.
61. The method of claim 39, wherein prior to the mapping, the method further comprises grouping sequencing reads based on (i) the identifier tag sequences and (ii) sequence information from the double-stranded DNA molecules, wherein a group comprises sequencing reads from the cypher-target amplification products of one of the cypher-target nucleic acid complexes.
62. The method of claim 39, wherein the cypher-target nucleic acid complexes comprise asymmetrical complexes having identifier tags of different lengths at each end.
63. The method of claim 39, wherein the cypher polynucleotides comprise a capture sequence and the sequencing comprises capturing the amplified cypher-target nucleic acid complexes on a solid surface comprising primers complementary to the capture sequence.
64. The method of claim 39, wherein the identifier tag sequences comprise random or partially random sequences.
65. The method of claim 64, wherein the random or partially random sequences comprise a length from about 5 nucleotides to about 50 nucleotides.
66. The method of claim 64, wherein the identifier tags are double-stranded sequences.
67. The method of claim 39, wherein the mutation, mutation distribution, mutation frequency, sequence heterogeneity, or DNA damage comprises a cancer biomarker.

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